38. (Amended) The method of claim 22 wherein the solvent in step (c) is selected from the group consisting of benzene, toluene, benzonitrile, *o*-xylene, *m*-xylene, [and] *p*-xylene, mesitylene, and diphenyl ether; the activated phosphite compound is selected from the group consisting of a mononucleotide phosphoramidite, a dinucleotide phosphoramidite, and a polynucleotide phosphoramidite; the protecting group of the 5'-O-protected nucleoside and the 5'-protected activated phosphite compound is dimethoxytrityl; the phosphorus linked oligomer is selected from the group consisting of a phosphodiester, phosphorothioate and a phosphorodithioate oligonucleotide; and the protic acid is dichloroacetic acid.

REMARKS

Claims **2, 6-7, 22, 24-25 and 38** stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims **2 and 22** stand rejected because the added step is allegedly not completely described. Although Applicants do not necessarily agree with the allegation, the claims have been amended to expedite prosecution. Claims **6-7, 22, 24-25 and 38** stand rejected for clerical errors and improper Markush groupings. The claims have been amended in accordance with the Examiner's suggestion.

The Office Action indicates that there is a technical misspelling in claims **13 and 30**. This has been corrected.

Claims 1-41 are rejected under 35 U.S.C § 103 (a) as being allegedly unpatentable over U.S. Patent No. 5,705,621 to Ravikumar ("Ravikumar") in view of U.S. Patent No. 4,973,679 to Caruthers et al. ("Caruthers") and further in view of U.S. Patent No. 5,548,076 to Froehler et al. ("Froehler") and further in view of Sproat et al. (PTO-892 Ref.

W), Conway et al. (PTO-892 Ref. Y), Atkinson et al. (PTO-892 Ref. Z), and Sproat et al. (PTO-892 Ref. RA).

None of the references alone or in combination teaches or suggests the present invention. The Office Action has failed to establish a *prima facie* case of obviousness. The present invention discloses novel features for the synthesis of oligonucleotides. Specifically, the present invention teaches the use of aromatic solvents for the deprotection step. Significantly, none of the references cited in the Office Action teach or suggest the use of aromatic solvents for the deprotection step.

Applicants concede that Ravikumar teaches certain conventional methods of oligonucleotide synthesis. However, none of the cited references teaches or suggests the modification of Ravikumar to employ aromatic solvents for the deprotection step taught by Ravikumar. As best understood by Applicants, the Office Action seems to suggest that the statement in Caruthers that "any organic solvents useful for *this reaction* include any solvent which will dissolve the reactants such as diethyl ether, chloroform, methylene chloride, ethylene chloride . . ." (emphasis added), in combination with Sproat (W), Conway, Atkinson, or Sproat (RA) suggests to one of skill in the art to use aromatic solvents for the coupling step. *However, the present invention is not directed to the use of aromatic solvents in the coupling reaction*. Rather, the present invention teaches the use of aromatic solvents in the *deprotection reaction*. The above-quoted statement in Caruthers refers to solvents used in the *coupling reaction* and not to solvents used in the deprotection step. Significantly, Caruthers teaches the use of $CDCl_3$ for the deprotection step, thereby teaching away from the present invention, which seeks to avoid the hazards and inefficiencies of the prior art processes which employ halogenated solvents such as chloroform.

Froehler fails to remedy the deficiencies of Ravikular and Caruthers. Although the Office Action states that Froehler teaches the use of ". . . an anhydrous organic solvent, preferably pyridine/acetonitrile . . .", Applicants fail to understand the relevance to

the present invention. The reference to pyridine/acetonitrile is directed to the *condensation reaction*. Significantly, there is no teaching or suggestion whatsoever in Froehler to employ aromatic solvents for the *deprotection reaction*, as contemplated by the present invention.

Neither Sproat (W), Conway, Atkinson, nor Sproat (RA), remedies the deficiencies of the above described references. Applicants agree that these references are each generally directed to oligonucleotide synthesis and that they teach that at various points in the synthetic process, some nucleotide and nucleoside derivatives are effectively dissolved in aromatic solvents (benzene and toluene). However, as discussed above, combination of these references with Caruthers and Froehler does not result in applicants claimed invention. Therefore, the Office Action fails to establish a *prima facie* case of obviousness.

Respectfully Submitted,

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